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### Authors

Korosi, Aniko  
Baram, Tallie Z

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## The central corticotropin releasing factor system during development and adulthood

**Aniko Korosi and Tallie Z. Baram**

*Departments of Anatomy / Neurobiology and Pediatrics, University of California Irvine, Irvine, CA, USA.*

### Abstract

Corticotropin releasing factor (CRH) has been shown to contribute critically to molecular and neuroendocrine responses to stress during both adulthood and development. This peptide and its receptors are expressed in the hypothalamus, as well as in limbic brain areas including amygdala and hippocampus. This is consistent with roles for CRH in mediating the influence of stress on emotional behavior and cognitive function.

The expression of CRH and of its receptors in hypothalamus, amygdala and hippocampus is age-dependent, and is modulated by stress throughout life (including the first postnatal weeks). Uniquely during development, the cardinal influence of maternal care on the central stress response governs the levels of central CRH expression, and may alter the 'set-point' of CRH-gene sensitivity to stress in a lasting manner.

### Keywords

corticotropin releasing factor; stress; neuroplasticity; development; maternal care; CRH receptor

### 1. Introduction

Corticotropin releasing factor (CRH) is mediator of endocrine, autonomic, and immune responses to stress (Vale et al., 1981; Owens and Nemeroff, 1991; De Souza, 1995; Holsboer and Barden, 1996; Brunson et al., 2001a). CRH has also been implicated in the modulation of a wide range of behaviors including anxiety, as well as in arousal, motor function (Dunn and Berridge, 1990), and learning and memory (Blank et al., 2002; Fenoglio et al., 2006a). In these capacities as a central neurotransmitter in distinct brain regions, CRH is involved in both normal brain function as well as in pathological conditions including anxiety, depression (Nemeroff and Vale, 2005) dementia (Behan et al., 1995; Brunson et al., 2001b; Rehman, 2002) and addiction (Koob, 2006).

Several groups have demonstrated release of endogenous CRH from neurons within amygdala (Merali et al., 1998; Herringa et al., 2006) hippocampus (Chen et al., 2004b, 2006a), locus coeruleus (Curtis and Valentino, 1994; Kirby et al., 2000) and cerebellum (King et al., 1997). However, much remains to be determined about the nature of the endogenous CRH- CRH receptor unit: how is the peptide released? From which neurons? From dendrites or axon

Corresponding author: Tallie Z. Baram, M.D., Ph.D., E-mail address: tallie@uci.edu; Tel.: +1-949-824-1063; fax: +1-949-824-1106; address: Med Sci I; ZOT 4475, University of California at Irvine, Irvine, California 92697-4475, USA.

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terminals? How does the peptide reach its receptors? Is CRH transported by volume transmission or is there a specific 'CRH synapse'? (Chen et al., 2004b). Where are the receptors located? What happens down-stream of CRH receptor activation? What is the role of the CRH-binding protein in the central CRH system? Clearly, many questions about the CRH system remain unanswered. Here we focus on the available information and delineate the central CRH system, highlighting the functions of this peptide within the central nervous system (CNS) both in the adult and the developing organism. The data suggests that during development, CRH has additional roles that influence long-lasting plasticity within the CNS.

## **2. What is the central CRH system? Neuroanatomical distribution of CRH-expressing neurons and of the CRH receptors**

### **2.1. CRH neuroanatomy**

CRH mRNA and protein are widely but specifically distributed throughout the CNS (Merchenthaler et al., 1982; Swanson et al., 1983; Keegan et al., 1994; Arborelius et al., 1999; Chen et al., 2001a). A major site of CRH-containing cell bodies is the parvocellular portion of the hypothalamic paraventricular nucleus where CRH acts as neurohormone (Sawchenko and Swanson, 1985; Swanson and Simmons, 1989). CRH-expressing axons originating in these neurons project to the median eminence, where CRH is stored in the external layer. Hypothalamic CRH-expressing neurons belong to both the 'peripheral' and 'central' stress systems: Stress-evoked release of the peptide governs secretion of adrenocorticotropin releasing hormone (ACTH) from the pituitary, contributing to the peripheral, neuroendocrine stress response. In addition, regulation of CRH expression in these cells may be involved in setting the 'tone' of stress-related behaviors including anxiety, as well as learning and memory (Plotsky and Meaney 1993; Avishai-Eliner et al., 2001a; Fenoglio et al., 2006b). Thus, the CRH cells in the hypothalamic paraventricular nucleus may also be considered part of the 'central' stress system.

The presence of CRH has been demonstrated in selective regions in the brain. The peptide is found in neocortex and in limbic regions including central nucleus of the amygdala, dorsal and ventral part of the bed nucleus of the stria terminalis and hippocampus. High densities of CRH-immunoreactive neurons reside in locus coeruleus, dorsal and median raphe, periaqueductal gray, nucleus of the solitary tract and cerebellar complex (Merchenthaler et al., 1982; Swanson et al., 1983; Sawchenko and Swanson, 1985; Sakanaka et al., 1987; Koegler-Muly et al., 1993; Van Bockstaele et al., 1996; King et al., 1997; Morin et al., 1999; Chen et al., 2004b). Here we focus on the distribution and function of CRH and its receptors, CRF<sub>1</sub> receptor and CRF<sub>2</sub> receptor, in selected regions including the hypothalamic paraventricular nucleus, hippocampal formation and amygdala nuclei.

### **2.2. CRH receptors: distribution and function**

CRH exerts its actions via a family of CRH receptors that includes two major characterized members: CRF<sub>1</sub> receptor and CRF<sub>2</sub> receptor (Perrin et al., 1993; Chalmers et al., 1995; Lovenberg et al., 1995), and CRF<sub>2</sub> receptor mRNA is translated in two functional splice variants, CRF<sub>2α</sub> receptor and CRF<sub>2β</sub> receptor. CRH receptors belong to the superfamily of G-protein-coupled receptors characterized by the presence of a seven transmembrane domain. CRH receptor binding causes activation of adenylyl cyclase through a stimulatory G protein, resulting in an increased production of cyclic adenosine monophosphate (cAMP) that subsequently binds to the regulatory subunit of phosphokinase A. The subunit then dissociates from the catalytic subunit, thereby activating it, which results in phosphorylation of numerous proteins (McKnight et al., 1988) including transcription factors (Gonzalez and Montminy, 1989). In addition to the cAMP pathway, other second messenger pathways involving mitogen-

activated protein kinase, calcium ions and phospholipase C have been implicated in the actions of CRH (Rossant et al., 1999; Blank et al., 2003).

CRF<sub>1</sub> receptor mRNA expression is widespread in mature rodent brain (Potter et al., 1994; Van Pett et al., 2000). Regions expressing the receptor include olfactory bulb, cerebral cortex, certain amygdala nuclei, hippocampus, globus pallidus, red nucleus, pontine gray, substantia nigra, sensory and motor trigeminal nuclei, and cerebellum. At the protein level, CRF<sub>1</sub> receptor immunoreactivity is found in a localization pattern that generally overlaps the target regions of CRH-expressing projections and the distribution of CRF<sub>1</sub> receptor mRNA (see Chen et al., 2000, for the mouse). The CRF<sub>2α</sub> receptor variant has been found in the CNS, where its distribution is more restricted than that of CRF<sub>1</sub> receptor. This receptor is found primarily in lateral septum, ventromedial hypothalamus, amygdala, dorsal raphe and bed nucleus of the stria terminalis (Van Pett et al., 2000). The CRF<sub>2β</sub> receptor variant is mainly present in non-neuronal cells, including in blood vessels (in brain and the periphery), heart, skeletal muscle and other organs.

The differential distribution of CRF<sub>1</sub> receptor and CRF<sub>2</sub> receptor already predicts that these receptors would exert different functions that are congruent with the established functions of the distinct brain regions where each one is located. Indeed, studies using mice deficient in one or both of these receptors, and those using selective receptor antagonists, have provided information about the distinctive function of the two CRH receptors. Thus, CRF<sub>1</sub> receptor is involved in the acute phase of the stress response, i.e., the activation of the hypothalamo-pituitary-adrenal (HPA) axis, whereas CRF<sub>2</sub> receptor seems to contribute to the recovery phase that involves gradual reduction of HPA axis activation (Coste et al., 2001; Reul and Holsboer, 2002). This idea is corroborated by the fact that CRF<sub>2</sub> receptor-knockout mice are hypersensitive to stress and have an increased anxiety-like behavior (Bale et al., 2000; Coste et al., 2000). For CRF<sub>2</sub> receptor, endogenous ligands might include, in addition to CRH, other members of the CRH family of peptides, including Urocortin 1 (Vaughan et al., 1995), that might thus contribute to the recovery phase of the stress response (Kozicz et al., 2004; Korosi et al., 2005).

### 3. Developmental neuroanatomy and regulation of CRH in rodent brain: hypothalamus

In view of the essential role of the stress response for normal function of the organism, a coordinate, progressive development of the stress circuit is required. Several studies in humans have demonstrated that early life trauma, such as childhood abuse or neglect, has lasting effects on parameters of the neuroendocrine stress circuit, and conveys major risk for the development of mood and anxiety disorders (Agid et al., 2000; Welberg and Seckl, 2001; Charney and Manji, 2004; Nemeroff, 2004). To understand the underlying mechanisms of vulnerability to stress-related disease, it is essential to study the development of the central components of the stress system. Thus in the following paragraphs we focus on CRH and CRH receptor expression, regulation (by glucocorticoids, stress, handling and maternal deprivation) and function during development, highlighting the brain areas playing key roles in this system.

#### 3.1. The developmental profile and the regulation of CRH synthesis in the hypothalamic paraventricular nucleus

In rat, immunoreactive CRH is first found in fibers in the anterior region of the median eminence on day 18 of gestation (E18, Bugnon et al., 1982). Peptide expression increases, with a transient perinatal reduction (Bugnon et al., 1982; Daikoku and Hisano, 1992). CRH mRNA is first detectable in rat hypothalamic paraventricular nucleus on E17 (Grino et al., 1989; Baram and Lerner, 1991). In analogy to the CRH protein, hypothalamic paraventricular nucleus CRH

mRNA expression is robust during fetal days 18 and 19, decreases perinatally (fetal days 20 and 21, Grino et al., 1989; Baram and Lerner, 1991), and finally increases to reach adult levels by the end of the first postnatal week. In mouse hypothalamic paraventricular nucleus, CRH expression is first detected on E13.5, also decreases around the time of birth, then climbs to adult levels (Keegan et al., 1994; Schmidt et al., 2003).

### 3.2. Regulation of hypothalamic CRH expression by glucocorticoids

Onset of CRH synthesis and the levels of CRH mRNA in the hypothalamus during fetal life are not regulated by glucocorticoids (Baram and Schultz, 1990, 1992). In fact, manipulation of plasma corticosterone using pharmacological adrenalectomy (Plotsky and Sawchenko, 1987), despite the drastic reduction of glucocorticoid levels in the fetus and an increase in CRH mRNA in the pregnant dams, did not alter CRH gene expression in the fetal hypothalamus (Baram and Schultz 1990, 1992). This is fundamentally different from the well-documented negative feedback of glucocorticoids on CRH synthesis in adult (Herman et al., 1989; Imaki et al., 1991). The lack of alteration of CRH mRNA levels by glucocorticoid in the fetal rat is not due to the absence of glucocorticoid receptors because glucocorticoid receptor mRNA has been shown in the hypothalamic paraventricular nucleus as early as the 16<sup>th</sup> fetal day (Yi et al., 1994). The onset of glucocorticoid negative feedback effect on CRH gene expression commences at the end of the first postnatal week. This has been shown using both adrenalectomy (Grino et al., 1989) and by implanting corticosterone-containing cannula into the hypothalamic paraventricular nucleus (Yi and Baram, 1993).

### 3.3. Regulation of CRH expression by acute and recurrent acute stress in the hypothalamus

A major component of the mature stress response is the transient upregulation of hypothalamic CRH synthesis associated with expression of immediate early genes (Kovacs and Sawchenko, 1996). Stress leads to depletion of hypothalamic stores of CRH (Ixart et al., 1987) and to a compensatory increase of CRH mRNA levels in the hypothalamic paraventricular nucleus (Lightman and Harbuz, 1993). In immature brain, the first two postnatal weeks has been characterized by attenuated hormonal response and altered gene regulation. However throughout this period CRH is secreted in response to stimuli that are stressful to a neonatal rat (Yi and Baram, 1994), leading to elevation of plasma corticosterone. Starting (at the latest) on the sixth postnatal day, saline injection and cold exposure are capable of inducing rapid increase of CRH gene transcription within 2–15 minutes after the stimulus (Baram and Hatalski, 1998; Dent et al., 2000; Chen et al., 2001b). This activation of the CRH gene can be measured using heteronuclear CRH RNA, and, by the ninth postnatal day is sufficiently robust to result in increased steady-state CRH mRNA levels in the hypothalamic paraventricular nucleus (Yi and Baram, 1994; Hatalski et al., 1998; Dent et al., 2000; Chen et al., 2001b). Stress-induced activation of CRH mRNA transcription is consistent with compensatory upregulation of CRH gene transcription after enhanced secretion of the peptide from hypothalamic nerve terminals, as found in the mature rodent (Lightman and Young, 1989). In the immature rodent, acute stress-evoked CRH gene activation might be regulated by pCREB (Chen et al., 2001b), as found in the adult (Kovacs and Sawchenko, 1996), suggesting that *acute* stress regulates CRH gene transcription fundamentally in the same manner in immature and adult hypothalamic paraventricular nucleus. The effects of *recurrent* stress, however, differ by age: recurrent stress augments hypothalamic CRH levels in adult rodents (Harbuz and Lightman, 1989; Makino et al., 1995b). In contrast, recurrent cold stress in the immature (P10) rat results in hypothalamic paraventricular nucleus CRH expression levels that resemble those of unstressed controls (Hatalski et al., 1998). The mechanisms for this age-specific effect of recurrent stress are not fully resolved. Negative feedback via glucocorticoids, released upon the first stress, should suppress CRH expression, and are already functional at P10. However, the facilitatory effects of stress on CRH gene expression (Akana and Dallman, 1992, 1997),

acting likely via the amygdala (Bhatnagar and Dallman, 1998), may not be fully functional (Walker and Dallman, 1993; Brunson et al., 2001a).

Thus, acute stress activates neuroendocrine responses, including transcription of the CRH gene, throughout development. However, the regulation of CRH expression and function does differ in immature and adult rodents in response to several other stimuli, most notable of which is the exquisite and enduring response of the CRH gene to maternal care (Denenberg and Whimby, 1963; Levine, 1970, 1994; Avishai-Eliner et al., 1995; Vazquez, 1998; Eghbal-Ahmadi et al., 1999; van Oers et al., 1999; Dent et al., 2000; Brunson et al., 2001a; Sanchez et al., 2001; Fenoglio et al., 2006b).

### **3.4. Effect of maternal deprivation, handling and chronic early life stress on CRH expression and function in the hypothalamic paraventricular nucleus**

Early life experience induces enduring neuroplasticity of the HPA axis (Levine, 1957, 1967; Francis et al., 1999; Sanchez et al., 2001; Avishai-Eliner et al., 2002; Plotsky et al., 2005; Fenoglio et al., 2006b), including lasting alteration of the levels of CRH expression in the hypothalamic paraventricular nucleus. Several paradigms have been used to investigate the role of maternal input in these effects. These have either employed separation from the mother for up to 24 hours, or alteration of maternal behavior either by 'handling' or via limiting nesting materials for the dam during the first weeks of life.

1. Maternal separation for 24 h has been shown to either not influence (Avishai-Eliner et al., 1995), or reduce (Smith et al., 1997a) basal hypothalamic paraventricular nucleus CRH gene expression. In mice, CRH mRNA levels decrease after 8–24 h of deprivation (Schmidt et al., 2004). In response to acute stress, maternal deprivation leads to higher secretion of ACTH and glucocorticoid (Avishai-Eliner et al., 1995; Baram et al., 1997; van Oers et al., 1998; Dent et al., 2000) and rapid stress-induced transcription of the CRH gene (Baram and Hatalski, 1998; Dent et al., 2000).

2. Daily brief (15 min) separations from the mother between postnatal days 2–7 (Denenberg and Whimby, 1963), 2–9 (Avishai-Eliner et al., 2001a; Fenoglio et al., 2006b) or 2–21 (Levine, 1967; Plotsky and Meaney, 1993), result in an adult phenotype of reduced stress response (Levine, 1957; Plotsky et al., 2005), reduced basal expression of CRH in the hypothalamic paraventricular nucleus, and increased hippocampal expression of glucocorticoid receptor (Plotsky and Meaney, 1993; Avishai-Eliner et al., 2001a). Handling enhances dam-pup interaction by provoking maternal sensory stimulation of pups immediately after their return to the home cage (Brown et al., 1977; Fenoglio et al., 2006b). Enhanced maternal care, attributable to either natural variation (Liu et al., 1997; Caldji et al., 1998) or induced experimentally by handling (Plotsky and Meaney, 1993) has been shown to lower CRH expression in the hypothalamic paraventricular nucleus, reduce hormonal responses to stress, and increase hippocampal glucocorticoid receptor levels (Avishai-Eliner et al., 2001a), changes collectively termed reduced HPA axis tone. Further insight into the mechanisms by which handling (or maternal input) influences CRH gene expression and the HPA axis tone has come from the finding that CRH and glucocorticoid receptor expression changes do not develop together but arise sequentially. Reduction of CRH expression in hypothalamic paraventricular nucleus occurs already by P9, developing as the first change of the several that occur at different levels of the HPA axis (Avishai-Eliner et al., 2001a; Fenoglio et al., 2006b). This supports a role of this gene regulation in the molecular cascade bridging handling-evoked maternal care and long term neuroplasticity of the HPA axis. CRH downregulation however does not occur after single handling maneuver but requires recurrent handling, even though already a single handling event elicits a burst of maternal stimulation of the pups (Fenoglio et al., 2006b).



3. Chronic early life “emotional” stress: Limiting the amount of nesting material constitutes a continuous stressor for the dam, leading to fragmented maternal care, which, in turn, stresses the pups (Gilles et al., 1996; Avishai-Eliner et al., 2001b). Thus the use of this paradigm from P2–P9 constitutes a chronic psychological early life stress. In fact, this paradigm evokes changes in the pups that are typical for chronic stress (Avishai-Eliner et al., 2001b): increased plasma glucocorticoid, increased adrenal weight and modestly reduced body weight (Hauger et al., 1988; Harbuz et al., 1992; Anderson et al., 1993). By the end of this week of stress (P9) CRH mRNA expression in the hypothalamic paraventricular nucleus of the early life stress group is significantly reduced compared to undisturbed controls both in rats (Avishai-Eliner et al., 2001b) and mice (Burgdorff et al., Soc. Neurosci. Abst, 2007). Reduced CRH expression may involve altered glucocorticoid negative feedback and/or increased CRH release concomitant with a failure of acute stress-induced facilitation of CRH production (Avishai-Eliner et al., 2001b). This depletion of hypothalamic CRH mRNA in the chronically stressed immature rodent differs from the adult situation (increased, decreased or unchanged, depending on the stress paradigm; Hauger et al., 1988; Harbuz et al., 1992; Anderson et al., 1993), indicating that the stage of development of the limbic-hypothalamic-pituitary-adrenal axis plays a critical role in the processes triggered by this chronic stress. Showing this reduction of CRH expression already at P9 is consistent with the concept that immature rat has a more rapid time course of adaptation to chronic stress which may be specific to this age (Dallman, 2000).

#### 4. Developmental neuroanatomy and regulation of CRH in rodent brain: Hippocampus

While hypothalamic CRH plays a neuroendocrine role, activated upon physiological stressors (also referred to as ‘reactive’ and ‘physical’), in higher brain centers CRH is an important mediator of psychological stressors (also termed ‘anticipated’ and ‘emotional’; Herman and Cullinan, 1997). These stressors activate higher-order limbic pathways that contribute to the central stress circuit (Herman and Cullinan, 1997) which includes the amygdala (McGaugh et al., 1996; Hatalski et al., 1998; Dayas et al., 2001) and the hippocampus (Meijer and de Kloet, 1998; Deak et al., 1999; Hatalski et al., 2000; Kjelstrup et al., 2002; Joels et al., 2004; Herman et al., 2005; Chen et al., 2006a; McEwen and Milner, 2007; and many others). During acute challenge, stress signals converge on the amygdala (Roosendaal et al., 1997, 1998), and selected stress signals reach the hippocampus (Wang et al., 1998; Hatalski et al., 2000; Blank et al., 2002). The hippocampus has crucial roles in learning, memory storage and retrieval and other cognitive functions, so that the effects of stress on the integrity of hippocampal structure and function has received much attention, as described in other chapters in this volume. Here we focus on 1) the development and regulation of the hippocampal CRH (2) the role of CRH in the effects of stress on hippocampal structure and function, and the distinction between the persistent effects of early-life stress on hippocampus versus the generally reversible effects of stress on mature hippocampus.

##### 4.1 The developmental profile and regulation of CRH synthesis in hippocampus

Compared to the hypothalamus, CRH mRNA expression is low in developing hippocampus (Vazquez et al., 2006). However the increased resolution of immunocytochemistry has demonstrated that CRH immunoreactive neurons are present in the hippocampal formation of stress-free rats as early as P1 (Yan et al., 1998; Chen et al., 2001a). The number of CRH immunoreactive neurons increases progressively during postnatal development, peaking at P18 (Chen et al., 2001a). In adult hippocampus, most CRH expressing neurons are GABAergic (Swanson et al., 1983; Merchenthaler, 1984; Yan et al., 1998). CRH expressing interneurons are primarily basket cells that synapse on somata of hippocampal pyramidal neurons. This positions them strategically to significantly influence pyramidal cell activity and hippocampal

information flow. During development, a second, significant population of CRH expressing neurons can be distinguished, possessing the morphology of hippocampal Cajal-Retzius cells. Most of these non-GABAergic neurons disappear by the end of the second postnatal week (Chen et al., 2001a).

In adult rats, administration of the synthetic glucocorticoid dexamethasone does not influence CRH levels in hippocampus (Calogero et al., 1991), whereas steroid elimination via adrenalectomy significantly decreases CRH mRNA in immature CA1 neurons (Brunson et al., 2001b). CRH gene expression in adult hippocampus had not been found to correlate with stress (Makino et al., 1995a), but increases after kindling (Smith et al., 1997b). In the immature rat, prototypic physiological challenge that activates the HPA axis (cold exposure) does not alter CRH expression and does not induce fos expression in hippocampus. In contrast an up-regulation of hippocampal CRH mRNA has been shown following hyperthermia (Hatafski et al., 2000), that was associated with intense neuronal activation, and was blocked by the administration of sodium pentobarbital (a blocker of polysynaptic neurotransmission via interaction with the GABA<sub>A</sub> receptor; Hatafski et al., 2000). In concert with these observations, kindling and kainic acid-evoked seizures also increased CRH expression in hippocampus (Smith et al., 1997b). Psychological stress in adult (Smith et al., 1997a) and immature rat (Hatafski et al., 2000) increased CRH expression in hippocampus (Hatafski et al., 2000). These studies also demonstrate that hippocampal CRH expression is regulated independent of that in the hypothalamus.

Brunson and colleagues found that early-life chronic stress leads to enduring, life long elevation of CRH expression within the hippocampal CA3 area (Fenoglio et al., 2006a). Early life stress impairs hippocampus-mediated cognitive functions, and disrupts synaptic physiology and LTP (Brunson et al., 2005). One of the possible mediators of the effects of early life stress on hippocampal neurons is CRH. The notion that hippocampal CRH in immature rat may participate in the mechanism by which early life stress influences learning and memory long-term is supported by several lines of evidences. These include the age-specific abundance of CRH expressing neurons in the developing hippocampus, the chronic upregulation of hippocampal CRH expression by early life stress, and, as described in the paragraphs below, the release of hippocampal CRH by stress, the excitotoxic actions of this peptide on hippocampal dendrites and neurons, and abundance of CRH receptors during development.

#### 4.2. CRH as a mediator of the actions of stress on hippocampal function

Psychological stress induces the release of endogenous hippocampal CRH (Chen et al., 2004b). CRH released by stress leads to the activation, measured by immediate early gene expression, of CA3 pyramidal cells, implicating endogenous CRH in the mechanism by which stress influences hippocampal pyramidal neurons. CRH excites hippocampal neurons, as evident from both in *vitro* (Aldenhoff et al., 1983; Hollrigel et al., 1998) and in *vivo* studies (Ehlers et al., 1983; Marrosu et al., 1988; Baram et al., 1992). Indeed, CRH administration early in life (P10) recapitulates the cognitive and LTP effects of early-life stress (Brunson et al., 2001b). This decline in hippocampal function in the CRH treated animals was progressive, and worsened over time. Importantly, the effects of early-life CRH occurred also in rats that were adrenalectomized prior to the experiment and maintained on low physiological corticosterone levels (Brunson et al., 2001b). In conclusion, in hippocampus, CRH modulates synaptic neurotransmission and in turn expression of the CRH gene is controlled by hippocampal circuit activation. Thus, this peptide contributes both to reversible effects of adult chronic stress, and to the enduring effects of early-life chronic stress, on hippocampal function.



## 5. Developmental neuroanatomy and regulation of CRH in rodent brain: Amygdala

The central nucleus of the amygdala is a key regulator of the stress response (Gray and Bingaman, 1996). CRH expressing neurons are found in the amygdala nuclei which are key components of the limbic stress circuit (Merali et al., 2004; Herman et al., 2005). Stress triggers the release of endogenous CRH in central nucleus of the amygdala, because administration of CRH antagonist into amygdala can attenuate stress-induced behaviors (Roozendaal et al., 2002). CRH mRNA levels within the amygdala can be already detected at P6 and gradually increases with age (Vazquez et al., 2006).

### 5.1. Regulation of CRH expression in the central nucleus of the amygdala by glucocorticoids, ACTH and stress

Administration of exogenous ACTH, or increasing endogenous ACTH levels by adrenalectomy downregulate CRH mRNA in central nucleus of the amygdala in P9–P11 rats (Brunson et al., 2001a). The ACTH (4–10) fragment infused i.c.v. also reduced CRH mRNA expression in central nucleus of the amygdala, even though it was devoid of any effects on plasma corticosterone, indicating that decreased CRH mRNA expression induced by ACTH is independent of steroid mediated mechanisms, and likely involves activation of the melanocortin 4 receptor (Brunson et al., 2001a). Glucocorticoids increase CRH gene expression in central nucleus of the amygdala of mature (Makino et al., 1994) and developing rats (Grino et al., 1989; Yi et al., 1993; Hatalski et al., 1998). In adult rat, expression of CRH mRNA in central nucleus of the amygdala is responsive to acute stress (Kalin et al., 1994). In the immature rat a single acute stress does not alter central nucleus of the amygdala CRH expression (Hatalski et al., 1998; Vazquez et al., 2006), but repeated stress does (Hatalski et al., 1998).

### 5.2 Age-specific regulation of central nucleus of the amygdala CRH expression: handling and maternal deprivation

CRH in the central nucleus of the amygdala may contribute to the role of this region in the integration of sensory signals from the mother (Eghbal-Ahmadi et al., 1999; Sanchez et al., 2001; Fenoglio et al., 2006b). CRH expression in central nucleus of the amygdala is enhanced by daily handling already by P6. By P9, enduring up-regulation of CRH mRNA in central nucleus of the amygdala is associated with similar changes in the bed nucleus of the stria terminalis (Hatalski et al., 1998; Fenoglio et al., 2004). This increase in CRH expression in central nucleus of the amygdala on P9 is associated with the reduced CRH expression in hypothalamic paraventricular nucleus. Possible mechanism underlying this independent and opposite effect on the two nuclei are the elevated levels of glucocorticoid after handling on P9 (Fenoglio et al., 2004). In fact, elevated glucocorticoid levels increase central nucleus of the amygdala and decrease hypothalamic paraventricular nucleus CRH gene expression in mature (Swanson and Simmons, 1989; Makino et al., 1994; Palkovits et al., 1998) and developing rats (Grino et al., 1989; Yi et al., 1993; Hatalski et al., 1998). After handling, no long-term increase of central nucleus of the amygdala CRH mRNA was observed (Plotsky and Meaney, 1993; Avishai-Eliner et al., 2001a). CRH mRNA expression is not altered by 24 h maternal deprivation (Vazquez et al., 2006).

## 6. Developmental neuroanatomy and regulation of CRH receptors in rodent brain

Within the brain CRH is synthesized and released into synaptic spaces where it can activate its receptors; therefore, the actions of this neuronal effector may be modulated via alteration

of CRH receptor expression or binding capacity. Thus the developmental pattern of expression of CRH receptors, their regulation and binding properties through development provide useful information regarding modulation of age specific roles of CRH in different brain areas.

### 6.1. The developmental profile of the CRH receptors in the rat brain

CRF<sub>1</sub> receptor mRNA distribution during development reveals several distinctive spatial and temporal patterns (Avishai-Eliner et al., 1996). In hippocampal CA1, CA2 and CA3a maximal (300–600% of adult) CRF<sub>1</sub> receptor mRNA levels are found on P6. In the amygdala, CRH receptor mRNA levels peak on the P9 (180% adult values). In the fronto-parietal cortex, a steady decline from high P2 levels results in adult levels by day 12.

Expression of the second member of the CRH receptor family, CRF<sub>2</sub> receptor is evident between fetal day 16 and 19 in ventromedial hypothalamus, lateral septum, amygdala nuclei, frontal cortex and habenula. These are joined by P1 by several hippocampal fields. CRF<sub>2</sub> receptor expression is fairly constant throughout development in the majority of these regions (Eghbal-Ahmadi et al., 1998), in contrast with CRF<sub>1</sub> receptor. The initial expression of CRF<sub>2</sub> receptor in the ventromedial hypothalamus, preceding detectable mRNA signal for CRH itself in the hypothalamic paraventricular nucleus (Altman and Bayer 1986; Grino et al., 1989; Baram and Lerner, 1991) suggests that the CRF<sub>2</sub> receptor may serve functions that are independent from activation by CRH during the early developmental period (e.g., cellular growth and differentiation). Alternatively, the CRF<sub>2</sub> receptor may be activated by a non-CRH ligand (e.g., Urocortin 1; Vaughan et al., 1995).

### 6.2. Regulation of CRH receptor expression

Acute stress increases CRF<sub>1</sub> receptor mRNA expression in Hypothalamic paraventricular nucleus and supraoptic nuclei of mature rat (Luo et al., 1994; Makino et al., 1995a, 1997; Rivest et al., 1995; Bonaz and Rivest, 1998; Imaki et al., 2001), but not mouse (Imaki et al., 2003). Chronic stress reduces CRF<sub>1</sub> receptor mRNA in the hypothalamic paraventricular nucleus (Makino et al., 1995a; Iredale et al., 1996; Bonaz and Rivest, 1998). In immature rat, acute stress has a biphasic effect on CRF<sub>1</sub> receptor mRNA expression (Brunson et al., 2002) and chronic stress reduces expression of this receptor in CA1 and dentate gyrus (Avishai-Eliner et al., 2001b). CRF<sub>1</sub> receptor mRNA expression is upregulated in CA3 area of adult animals given CRH early in life (Brunson et al., 2001b). The reported effects of glucocorticoids on CRF<sub>1</sub> receptor mRNA expression in hypothalamic paraventricular nucleus are inconsistent (Makino et al., 1995a, 1997), but are generally in line with those of stress.

CRF<sub>2</sub> receptor mRNA in ventromedial hypothalamus is influenced by food deprivation in adults (Timofeeva and Richard, 1997; Makino et al., 1998), and reduced following maternal deprivation in infant rats (Eghbal-Ahmadi et al., 1997). However, during this age, maternal sensory input rather than food is the dominant regulator of this receptor's expression in ventromedial hypothalamus (Eghbal-Ahmadi et al., 1999). Glucocorticoids increase ventromedial hypothalamus CRF<sub>2</sub> receptor mRNA expression, but have no effect on expression of this gene in hypothalamic paraventricular nucleus (Makino et al., 1997, 1998).

CRH itself may control CRF<sub>1</sub> receptor and CRF<sub>2</sub> receptor expression. Thus, exogenous CRH stimulates transcription of CRF<sub>1</sub> receptor in adult hypothalamic paraventricular nucleus (Imaki et al., 1996; Mansi et al., 1996) and in developing hippocampus and frontal cortex (Brunson et al., 2002). Whereas CRH has little effect on adult (Mansi et al., 1996) or immature (Brunson et al., 2002) CRF<sub>2</sub> receptor expression in rat, the peptide may play a role in regulating both CRF<sub>1</sub> receptor and CRF<sub>2</sub> receptor mRNA expression in mouse (Korosi et al., 2006).

### 6.3. Age-specific functions of CRH receptors

Whether CRF<sub>1</sub> receptor and CRF<sub>2</sub> receptor have unique developmental roles in addition to their established function as transducers of the effects of CRH-family ligands, is not currently known (Schmidt et al., 2004, 2006). However, several pieces of evidence support this concept.

1. CRF<sub>1</sub> receptor: mice lacking this receptor have abnormal shape of hippocampal neurons. Specifically, dendritic trees are exuberant and complex (Chen et al., 2004a). Whereas the presence of these changes has not yet been demonstrated in fore-brain restricted null mice, a direct role for CRF<sub>1</sub> receptor is supported by the fact that these abnormal dendritic trees persist in organotypic slice cultures where glucocorticoid levels are irrelevant (Chen et al., 2006b). Thus, CRF<sub>1</sub> receptor may be involved in dendritic differentiation, perhaps pruning related to establishment or maintenance of synapses. The location of this receptor on dendritic spines, directly in the postsynaptic density supports this putative role of the receptor (Chen et al., 2004a,b).

2. CRF<sub>2</sub> receptor: the only information available to the authors about development-specific functions of this receptor is the curious early onset of its expression in ventromedial hypothalamus (see above). Much remains to be studied about the function of these prenatal CRF<sub>2</sub> receptors in the developing hypothalamus.

## 7. General conclusions

CRH is a key contributor to the repertoire of factors regulating the mammalian response to stress, complementing the actions of glucocorticoids and sympathetic neurotransmitters. In the spatial domain, because the peptide is released from local neurons, it can mediate rapidly the effects of acute stress on specific neuronal populations. Thus, local CRH release in amygdala (Roosendaal et al., 2002) or hippocampus (Chen et al., 2004b, 2006a) can activate selected neuronal populations that carry CRF receptors. In the temporal domain, being a neuropeptide, CRH acts within seconds and exert effects over minutes-to hours, bridging the actions of neurotransmitters (seconds to minutes) and hormones (generally several hours). As highlighted in the current chapter, the central CRH system is very active early in life. During this period, altered regulation of CRH expression levels by early life experiences (handling, chronic early life stress) may last for the duration of the animal's life. Indeed, CRH gene regulation, likely epigenetic, constitutes a major molecular cascade for the long-lasting neuroplasticity of stress response reactivity and cognitive and emotional function later in life.

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